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Title: Commonly prescribed antiretroviral therapy regimens and incidence of AIDS-defining neurological conditions

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Abstract

Background: The differential effects of commonly prescribed combined antiretroviral therapy (cART) regimens on AIDS-defining neurological conditions (neuroAIDS) remain unknown.

Setting: Prospective cohort studies of HIV-positive individuals from Europe and the Americas included in the HIV-CAUSAL Collaboration.

Methods: Individuals who initiated a first-line cART regimen in 2004 or later containing a nucleoside reverse transcriptase inhibitor (NRTI) backbone and either atazanavir, lopinavir, darunavir, or efavirenz were followed from cART initiation until death, lost to follow-up, pregnancy, the cohort-specific administrative end of follow-up, or the event of interest, whichever occurred earliest. We evaluated four neuroAIDS conditions: HIV dementia and the opportunistic infections toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy. For each outcome, we estimated hazard ratios for atazanavir, lopinavir, and darunavir compared with efavirenz via a pooled logistic model. Our models were adjusted for baseline demographic and clinical characteristics.

Results: 26,172 individuals initiated efavirenz, 5,858 initiated atazanavir, 8,479 initiated lopinavir, and 4,799 initiated darunavir. Compared with efavirenz, the adjusted HIV dementia hazard ratios (95% CIs) were 1.72 (1.00, 2.96) for atazanavir, 2.21 (1.38, 3.54) for lopinavir, and 1.41 (0.61, 3.24) for darunavir. The respective hazard ratios (95% CIs) for the combined endpoint were 1.18 (0.74, 1.88) for atazanavir, 1.61 (1.14, 2.27) for lopinavir, and 1.36 (0.74, 2.48) for darunavir. The results varied in subsets defined by calendar year, NRTI backbone, and age.

Conclusion: Our results are consistent with an increased risk of neuroAIDS after initiating lopinavir compared with efavirenz, but temporal changes in prescribing trends and confounding by indication could explain our findings.

Keywords: HIV, HIV dementia, Antiretroviral Therapy, neuroAIDS

Introduction

As the life-expectancy of individuals living with HIV increases, more research is needed to understand the impact of HIV and combined antiretroviral therapy (cART) on neurodegeneration, cognitive decline, and aging in general [1-3]. While the incidence of AIDS-defining neurological conditions (neuroAIDS) in high-income countries decreased after the introduction of cART [4-7], the potential for differential effects of commonly prescribed cART regimens on neuroAIDS has not been well evaluated.

Clinical guidelines for HIV-positive individuals recommend ritonavir-boosted protease inhibitor (bPI)-based regimens [8-10] and non-nucleoside reverse transcriptase inhibitor (NNRTI)- based regimens [10] as first-line regimens in addition to the newer Integrase Strand Transfer Inhibitor (InSTI) regimens. Commonly prescribed bPIs include atazanavir, lopinavir, and darunavir and

one of the most commonly prescribed NNRTIs is efavirenz. While recent guidelines have shifted to recommend InSTI regimens over other regimens as first-line regimens, switching from other regimens to InSTI regimens is currently not recommended unless an individual experiences virologic failure or drug-related toxicity. However, switching for regimen simplification, personal preference, or after diagnosis with a co-morbidity also occurs. Since cART is life-long, many individuals who initiated bPI and NNRTI based regimens in the cART era could remain on these regimens for the long-term.

cART regimens with high penetration into the central nervous system (CNS) more effectively target HIV replication in the brain. Previous studies of the relationship between cART and neuroAIDS have focused on antiretroviral CNS penetration rather than specific drug regimens. These studies have had conflicting results [7, 11-13] and the clinical relevance of the CNS penetration ranking system is questionable [7]. To our knowledge, no studies have compared the effect of different cART regimens on neuroAIDS.

Here, we use data from prospective cohort studies of HIV-positive individuals in Europe and the Americas to investigate the potential effect of commonly prescribed cART regimens on clinical diagnoses of four neuroAIDS conditions: HIV dementia and the opportunistic infections toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy.

Methods

Study population

The HIV-CAUSAL Collaboration includes prospective cohort studies from 6 European countries and the Americas [14]. The individual cohort studies are French Hospital Database-ANRSC04 (France), ANRS PRIMO (France), ANRS SEROCO (France), ANRS CO3-Aquitaine (France),

UK CHIC (United Kingdom), UK Register of HIV Seroconverters (United Kingdom), ATHENA (the Netherlands), Swiss HIV Cohort Study (Switzerland), PISCIS (Spain), CoRIS/CoRIS-MD (Spain), GEMES (Spain), VACS (United States), AMACS (Greece), IPEC (Brazil) and Southern Alberta Cohort (Canada). Each cohort was assembled prospectively and is based on data collected for clinical purposes. All cohorts included in the HIV-CAUSAL Collaboration collected data prospectively, including all CD4 cell counts, HIV RNA measurements, treatment initiations, deaths, and AIDS-defining illnesses (including the events of interest).

Our analysis was restricted to previously antiretroviral therapy-naïve HIV-positive individuals who initiated a first-line cART regimen in 2004 or later containing a nucleoside reverse transcriptase inhibitor (NRTI) backbone and either boosted atazanavir, boosted lopinavir, boosted darunavir, or efavirenz. Only a small number of individuals started cART with InSTI or a fusion inhibitor and were therefore excluded. Individuals who initiated an NNRTI other than efavirenz, a bPI other than atazanavir, lopinavir, or darunavir, or more than one of the drugs listed previously were also excluded. Our analysis was further restricted to individuals who met the following criteria at the date of cART initiation (baseline): age 18 years or older, no pregnancy (when information was available), no history of AIDS (defined as the onset of any CDC Classification Category C AIDS-defining illness), and CD4 cell count and HIV RNA measured within the previous six months. Individuals were required to start all of the drugs in their first-line cART regimen within the same calendar month. Individuals who changed or discontinued antiretroviral therapy remained classified by their initial regimen as it would have been done in an intention-to-treat analysis of a randomized trial.

We allowed regimens to be paired with all NRTI backbones in our main analysis but restricted the analysis to NRTI backbones appearing in the most recent guidelines in subgroup analyses.

Specifically, we focused on the backbones abacavir/lamivudine, tenofovir/emtricitabine, and tenofovir/lamivudine.

We conducted separate analyses for HIV dementia, toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy. Since the opportunistic infections were relatively rare and some mechanisms through which cART regimens may affect opportunistic infections could overlap, we also considered a combined endpoint of any of the three opportunistic infections. The date of neuroAIDS was identified by the treating physicians. One of the contributing cohorts (VACS) used ICD-9 codes to identify incident neuroAIDS cases. The other contributing cohorts used diagnostic procedures that reflect standard clinical practice rather than standardized research criteria. Non-Hodgkin lymphoma was not included as an outcome because in most cases it was not possible to differentiate primary brain lymphoma from other types of non-Hodgkin lymphoma. Other HIV-associated neurocognitive disorders including mild neurocognitive disorder and asymptomatic neurocognitive impairment were not included because this information was not usually recorded in the medical records. Individuals were followed from baseline until death, 12 months after the most recent laboratory measurement, pregnancy (if known), the cohort-specific administrative end of follow-up (ranging from December 2009 to November 2015), or the event of interest, whichever occurred first.

Statistical methods

We used a pooled logistic regression model to estimate neuroAIDS hazard ratios for each cART regimen versus efavirenz. A separate model was fit for each neuroAIDS condition as well as for the combined endpoint. The model included an indicator for the cART regimen, month of follow-up (restricted cubic splines with 4 knots at 1, 6, 24, and 60 months) and the following covariates at cART initiation: CD4 cell count (<200, 200-299, 300-399, ≥400 cells/µl), HIV-

RNA (<10,000, 10,000-100,000, >100,000 copies/ml), sex, race (white, black, other or unknown), geographic origin (Western countries, sub-Saharan Africa, other, or unknown), calendar year (2004-2007, ≥2008), mode of HIV acquisition (heterosexual, homosexual/bisexual, injection drug use, other or unknown), years since HIV diagnosis (<1, 1-4, ≥5 years or unknown), cohort region, and age (<35, 35-49, ≥50 years).

We performed several subset and sensitivity analyses. We restricted our analyses to individuals initiating cART in 2008 or later, to individuals 50 years of age or younger at cART initiation, to individuals with CD4 cell count less than or equal to 400 cells/µl at cART initiation, to individuals diagnosed with HIV within the previous 5 years, to individuals from western countries, to men, and to those whose acquisition group was other than injection drug use. Since individuals who were lost to follow-up might be different from those who remained in the study, we used inverse probability (IP) weighting to adjust for potential selection bias due to infrequent laboratory measurements. Each patient received a time-varying weight inversely proportional to the estimated probability of not being censored, for each month that patient was followed. To estimate the weights, we fit a pooled logistic model using the baseline covariates listed above as well as the most recent measurement of the time-varying covariates CD4 cell count (restricted cubic splines with 5 knots at 10, 200, 350, 500, and 1000 cells/µl), HIV RNA (<10,000, 10,000-100,000, >100,000 copies/ml), time since last laboratory measurement (0, 1-2, 3-4, 5-6, >6 months), and AIDS [15, 16]. We also weighted by the inverse probability of remaining alive as a form of competing risks analysis [17]. Finally, we excluded efavirenz regimens from the analysis since individuals initiating efavirenz regimens may be different than individuals initiating other regimens in ways related to the outcomes and compared lopinavir and darunavir regimens to atazanavir regimens.

All analyses were conducted with SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

Ethical Approval

Research using the HIV-CAUSAL Collaboration was determined to be non-human subjects research by the Institutional Review Board of the Harvard T.H. Chan School of Public Health because it involves the study of existing data that is analyzed in such a manner that the subjects cannot be identified, as set forth in U.S. federal regulations. Written informed consent from patients was not required as all data was completely anonymized.

Results

Of 45,308 individuals who initiated cART in 2004 or later, 26,172 initiated an efavirenz regimen, 5,858 initiated an atazanavir regimen, 8,479 initiated a lopinavir regimen, and 4,799 initiated a darunavir regimen. Compared with efavirenz, atazanavir, and darunavir, those initiating lopinavir had lower baseline CD4 cell counts and were more likely to be women, have heterosexual condomless sex as their mode of HIV acquisition, and have initiated cART before 2008 (Table 1). The median (IQR) baseline CD4 cell count at cART initiation was 208 (106, 291) cells/µl among individuals initiating cART prior to 2008 and 270 (170, 358) cells/µl among individuals initiating cART in 2008 or later.

Over the follow-up period, there were 113 cases of HIV dementia, 201 cases of the combined endpoint of any neuroAIDS opportunistic infection, 89 cases of toxoplasmosis, 46 cases of cryptococcal meningitis, and 69 cases of progressive multifocal leukoencephalopathy. 16 individuals developed two of the four neuroAIDS conditions and 1 individual developed three. The median (IQR) follow-up time was 37 (20, 64) months in the HIV dementia analysis and was similar in the other analyses. Among those with the event, the median (IQR) time to event ranged

from 3 (1, 7) months for progressive multifocal leukoencephalopathy to 8 (2, 23) months for HIV dementia. Compared with efavirenz, the HIV dementia hazard ratios were 1.72 (1.00, 2.96) for atazanavir, 2.21 (1.38, 3.54) for lopinavir, and 1.41 (0.61, 3.24) for darunavir. Compared with efavirenz, the hazard ratios for the combined endpoint were 1.18 (0.74, 1.88) for atazanavir, 1.61 (1.14, 2.27) for lopinavir, and 1.36 (0.74, 2.48) for darunavir. The hazard ratios comparing each cART regimen with efavirenz for the individual opportunistic infections were close to 1.00 for toxoplasmosis and cryptococcal meningitis, but ranged from 1.46 (0.54, 3.93) (darunavir) to 2.16 (1.17, 3.98) (lopinavir) for progressive multifocal leukoencephalopathy (Table 2). In general, these hazard ratios were attenuated compared with the unadjusted estimates. For the combined endpoint, the median (IQR) CD4 cell count at the time of event was 134 (52, 266) cells/µl for atazanavir, 72 (29, 161) cells/µl for efavirenz, 75 (30, 190) cells/µl for lopinavir, and 108 (49, 179) cells/µl for darunavir.

Figure 1 compares the neuroAIDS hazard ratios estimated for all NRTI backbones to those estimated when the analysis was restricted to tenofovir/emtricitabine backbones as well as any of the following NRTI backbones: tenofovir/emtricitabine, tenofovir/lamivudine, and abacavir/lamivudine (essentially excluding backbones containing zidovudine). When restricting to these NRTI backbones, the HIV dementia hazard ratio was attenuated for atazanavir but not for lopinavir, and the hazard ratios for the combined endpoint were largely unchanged.

When we restricted the analysis to the 29,180 (64%) individuals who initiated cART in 2008 or later the hazard ratios were attenuated for HIV dementia, but not for the combined endpoint (Figure 2). When we restricted the analysis to individuals who were 50 years of age or younger at baseline the HIV dementia hazard ratios comparing atazanavir and lopinavir with efavirenz were larger than in the primary analysis, but the estimates for the combined endpoint were

attenuated (Figure 2). The confidence intervals in these sensitivity analyses were wide and there were too few events to look at each opportunistic infection separately. Our results were similar when we used continuous as opposed to categorical baseline variables. None of the other sensitivity analyses described previously yielded appreciably different results.

In the analysis excluding efavirenz regimens, the HIV dementia hazard ratios were 1.18 (0.64, 2.19) for lopinavir and 0.96 (0.39, 2.37) for darunavir, compared with atazanavir. The hazard ratios for the combined endpoint were 1.52 (0.93, 2.50) for lopinavir and 1.12 (0.55, 2.31) for darunavir, compared with atazanavir (Figure 2).

Discussion

Our study is the first to examine potential differences by cART regimen on the risk of clinical diagnoses of neuroAIDS. Our findings are consistent with an increased risk of HIV dementia after initiating cART regimens containing lopinavir or atazanavir and with an increased risk of neuroAIDS opportunistic infections after initiating cART regimens containing lopinavir, compared with efavirenz. However, our findings need to be interpreted with caution because a large proportion of the cases were diagnosed within a few months of initiation and the increased relative risk was substantially attenuated among individuals initiating cART in 2008 or later. It is therefore possible that the increased risk found in our main analysis could be due to changes in prescribing trends over time such as prescribing zidovudine as an NRTI backbone, prescribing InSTI-based regimens to individuals who could be at higher risk for neuroAIDS, or starting cART at higher CD4 levels.

To the extent that our estimates were causal, possible mechanisms through which cART regimens could affect the incidence of neuroAIDS include penetration of antiretrovirals into the

CNS, level of HIV-RNA suppression, and immunologic recovery, but are not fully understood. cART regimens with greater penetration into the CNS could decrease the risk of HIV dementia by more effectively targeting HIV replication in the brain, but could also increase HIV dementia risk via deposition of beta-amyloid plaques into the brain [7, 18]. However, since lopinavir and efavirenz have the same CNS penetration effectiveness rankings [12], CNS penetration may not explain our findings. An effect of cART regimens on HIV dementia could also be explained by differences in HIV-RNA replication or lipid profile [19] after cART initiation. On the other hand, any effect of cART regimens on opportunistic infections is more likely explained by differences in CD4 cell count recovery after cART initiation [5, 20]. Randomized trials comparing lopinavir with efavirenz have found no difference in CD4 cell count recovery 48 weeks after cART initiation [21], a smaller proportion of individuals achieving virologic suppression at 48 weeks [21] and 96 weeks [22], and a greater increase in triglyceride levels [21]. In our study, the CD4 cell count at the time of event for the combined endpoint was similar for lopinavir compared with efavirenz.

A causal interpretation of our findings relies on the untestable assumption that the measured covariates were sufficient to adjust for confounding. Confounding by indication might partly explain our estimates if efavirenz was prescribed less frequently to individuals at higher risk for neuroAIDS. Efavirenz is often avoided in individuals with a history of mental health problems and depression and psychiatric and nervous system symptoms have been reported more frequently in individuals treated with efavirenz, although efavirenz is not contraindicated for individuals at higher risk for neurologic conditions [23]. Individuals who initiated lopinavir in our study differed from individuals who initiated other regimens with respect to calendar year and key clinical and demographic factors, suggesting that they could also differ with respect to

unmeasured lifestyle, social, and behavioral factors for which we were not able to adjust such as depression, education level, and cardiovascular disease. In general, the unadjusted estimates from our analysis were larger than the adjusted estimates; however, the direction of any remaining unmeasured confounding is unknown.

Our results could also be biased if there are diagnostic delays for the outcomes of interest that are differential with respect to cART regimen. While we did not have information on the frequency of neurologic screening in our study, we found no differences by cART regimen for frequency of CD4 and HIV-RNA monitoring, which may serve as a proxy for frequency of encounters with a medical provider.

Our findings are consistent with an increased risk of neuroAIDS after initiating cART regimens with lopinavir compared with efavirenz, but a causal interpretation is not warranted. The increased risk was diminished in more recent years, perhaps due to individuals initiating cART at higher CD4 cell counts or other changes in prescribing patterns, and confounding by indication is a more likely explanation for our findings. Given the direction of our estimates, our study provides moderate evidence against a negative effect of efavirenz regimens compared with other cART regimens commonly prescribed in the same era on neuroAIDS. Efavirenz is a drug that remains commonly prescribed but for which neurologic effects have been a concern. Our study may be useful in informing the design of randomized clinical trials to evaluate the comparative effectiveness of cART regimens on neurologic outcomes.

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Figure 1: NeuroAIDS outcomes by recommended NRTI backbone, HIV-CAUSAL Collaboration 2004-2015.

*Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis).
TDF, tenofovir; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir. Full results in Appendix Table 1 and Appendix Figure 1.

Figure 2: NeuroAIDS outcomes by subgroup (left) and excluding efavirenz (right), HIV-CAUSAL Collaboration 2004-2015.

*Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis).

cART initiation ≥2008, analysis restricted to individuals initiating cART in 2008 or later
Baseline age≤50, analysis restricted to individuals less than 50 years at baseline
Full results in Appendix Table 2 and Appendix Table 3.

Table 1. Characteristics of 45,308 antiretroviral therapy-naïve HIV-positive individuals at baseline by type of initial cART regimen, HIV-CAUSAL Collaboration, 2004-2015.

Characteristic		Efavirenz (n=26,172)		Atazanavir (n=5,858)		Lopinavir (n=8,479)		Darunavir (n=4,799)	
Sex	Men	22,442	(85.8)	4,640	(79.2)	5,920	(69.8)	4,087	(85.2)
	Women	3,730	(14.3)	1,218	(20.8)	2,559	(30.2)	712	(14.8)
Age, years	< 35	9,146	(35.0)	1,964	(33.5)	3,133	(37.0)	1,710	(35.6)
	35 – 50	12,175	(46.5)	2,746	(46.9)	3,895	(45.9)	2,212	(46.1)
	> 50	4,851	(18.5)	1,148	(19.6)	1,451	(17.1)	877	(18.3)
Geographic origin	Western countries	13,542	(51.7)	3,572	(61.0)	5,082	(59.9)	3,026	(63.1)
	Sub-Saharan Africa	1,439	(5.5)	507	(8.7)	1,342	(15.8)	336	(7.0)
	Other	2,786	(10.6)	523	(8.9)	831	(9.8)	403	(8.4)
	Unknown	8,405	(32.1)	1,256	(21.4)	1,224	(14.4)	1,034	(21.6)
Acquisition group	Heterosexual	7,621	(29.1)	1,985	(33.9)	3,972	(46.9)	1,345	(28.0)
	Homosexual	12,808	(48.9)	2,500	(42.7)	2,797	(33.0)	2,699	(56.2)
	Injection drug use	688	(2.6)	262	(4.5)	545	(6.4)	197	(4.1)
	Other/Unknown[a]	5,055	(19.3)	1,111	(19.0)	1,165	(13.7)	558	(11.6)
CD4 cell count, per mm^3	< 200	8,108	(31.0)	1,870	(31.9)	4,057	(47.9)	1,481	(30.9)
	200 – 299	7,488	(28.6)	1,524	(26.0)	2,026	(23.9)	908	(18.9)
	300 – 399	5,951	(22.7)	1,295	(22.1)	1,203	(14.2)	1,032	(21.5)
	≥ 400	4,625	(17.7)	1,169	(20.0)	1,193	(14.1)	1,378	(28.7)
HIV RNA, copies/mL	< 10,000	4,682	(17.9)	1,105	(18.9)	1,512	(17.8)	720	(15.0)
	10,000 – 100,000	11,776	(45.0)	2,571	(43.9)	3,102	(36.6)	1,825	(38.0)
	> 100,000	9,714	(37.1)	2,182	(37.3)	3,865	(45.6)	2,254	(47.0)

Race	White	6,464	(24.7)	1,344	(22.9)	1,474	(17.4)	1,577	(32.9)
	Black	2,484	(9.5)	400	(6.8)	555	(6.6)	258	(5.4)
	Other/Unknown	17,224	(65.8)	4,114	(70.2)	6,450	(76.1)	2,964	(61.8)
Years since HIV diagnosis	< 1	12,660	(48.4)	2,737	(46.7)	5,114	(60.3)	2,809	(58.5)
	1 – 4	7,798	(29.8)	1,649	(28.2)	1,767	(20.8)	964	(20.1)
	≥ 5 or unknown	5,714	(21.8)	1,472	(25.1)	1,598	(18.9)	1,026	(21.4)
Calendar year	2004 – 2007	8,186	(31.3)	1,512	(25.8)	4,787	(56.5)	22	(0.5)
	≥ 2008	17,986	(68.7)	4,346	(74.2)	3,692	(43.5)	4,777	(99.5)
Cohort	UK CHIC	7,254	(27.7)	1,079	(19.4)	905	(10.7)	825	(17.2)
	ATHENA	3,479	(13.3)	572	(9.8)	677	(8.0)	520	(10.8)
	FHDH-ANRS CO4	3,144	(12.0)	1,668	(28.5)	3,175	(37.5)	1,095	(22.8)
	Aquitaine	231	(0.9)	107	(1.8)	253	(3.0)	57	(1.2)
	SHCS	1,071	(4.1)	356	(6.1)	486	(5.7)	442	(10.4)
	PISCIS/AMACS	2,661	(10.2)	639	(10.9)	1,108	(13.1)	499	(10.4)
	CoRIS	2,751	(10.5)	353	(6.0)	755	(8.9)	568	(11.8)
	Seroconverters[b]	785	(3.0)	183	(3.1)	280	(3.3)	463	(9.7)
	VACS-VC	3,509	(13.4)	745	(12.7)	525	(6.2)	226	(4.7)
	IPEC	985	(3.8)	126	(2.2)	112	(1.3)	0	(0)
	SAC	302	(1.2)	30	(0.5)	203	(2.4)	104	(2.2)

[a] Other/Unknown acquisition group included all VACS-VC participants.

[b] Includes the UK Register of HIV Seroconverters, ANRS PRIMO, and GEMES (Grupo Español Multicéntrico para el Estudio de Seroconvertores-Hemofilia) cohorts

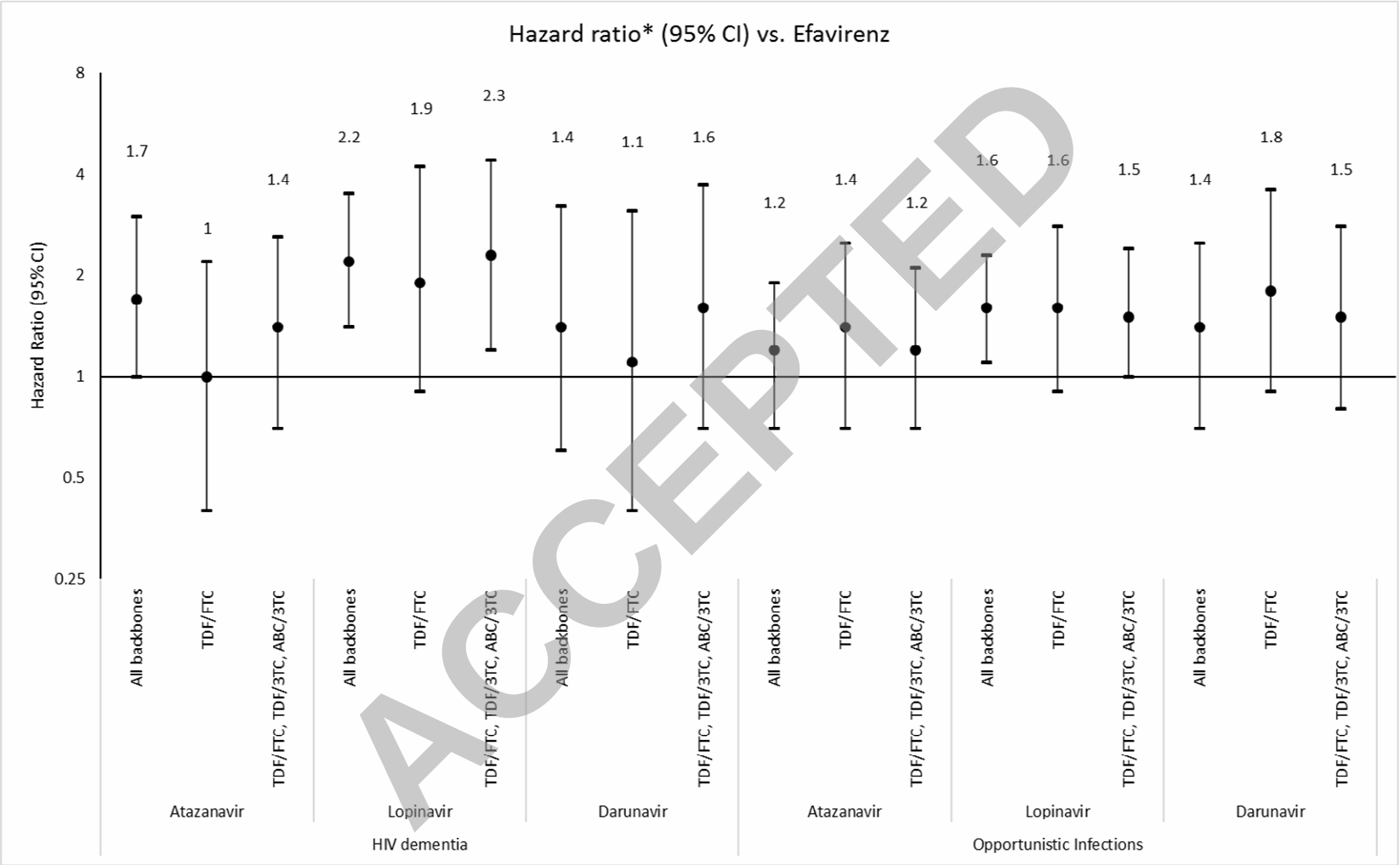
Table 2. NeuroAIDS outcomes for regimens based on atazanavir, lopinavir, and darunavir versus efavirenz, HIV-CAUSAL Collaboration 2004-2015

NeuroAIDS event	Treatment	Person-years	No. of events	Unadjusted hazard ratio	95% CI	Adjusted hazard ratio[b]	95% CI
HIV dementia	Efavirenz	100,979	49	1.00	reference	1.00	reference
	Atazanavir	19,010	19	1.79	1.05, 3.05	1.72	1.00, 2.96
	Lopinavir	36,298	38	2.90	1.83, 4.59	2.21	1.38, 3.54
	Darunavir	9,680	7	1.40	0.62, 3.18	1.41	0.61, 3.24
Opportunistic infections[a]	Efavirenz	100,803	90	1.00	reference	1.00	reference
	Atazanavir	18,968	22	1.09	0.68, 1.73	1.18	0.74, 1.88
	Lopinavir	36,190	76	2.39	1.73, 3.28	1.61	1.14, 2.27
	Darunavir	9,674	13	0.96	0.54, 1.72	1.36	0.74, 2.48
Toxoplasmosis	Efavirenz	100,987	40	1.00	reference	1.00	reference
	Atazanavir	19,003	9	0.95	0.47, 1.91	1.11	0.54, 2.26
	Lopinavir	36,314	34	2.05	1.27, 3.30	1.41	0.84, 2.37
	Darunavir	9,683	6	0.86	0.37, 1.99	1.27	0.52, 3.06
Cryptococcal meningitis	Efavirenz	101,033	26	1.00	reference	1.00	reference
	Atazanavir	19,038	4	0.71	0.25, 2.07	0.73	0.25, 2.17
	Lopinavir	36,392	14	1.78	0.91, 3.47	1.21	0.59, 2.45
	Darunavir	9,690	2	0.78	0.18, 3.32	1.28	0.28, 5.92
Progressive multifocal leukoencephalopathy	Efavirenz	100,990	26	1.00	reference	1.00	reference
	Atazanavir	19,017	10	1.78	0.85, 3.73	1.84	0.88, 3.83
	Lopinavir	36,387	28	3.18	1.83, 5.51	2.16	1.17, 3.98
	Darunavir	9,684	5	1.16	0.44, 3.09	1.46	0.54, 3.93

a. Includes toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy

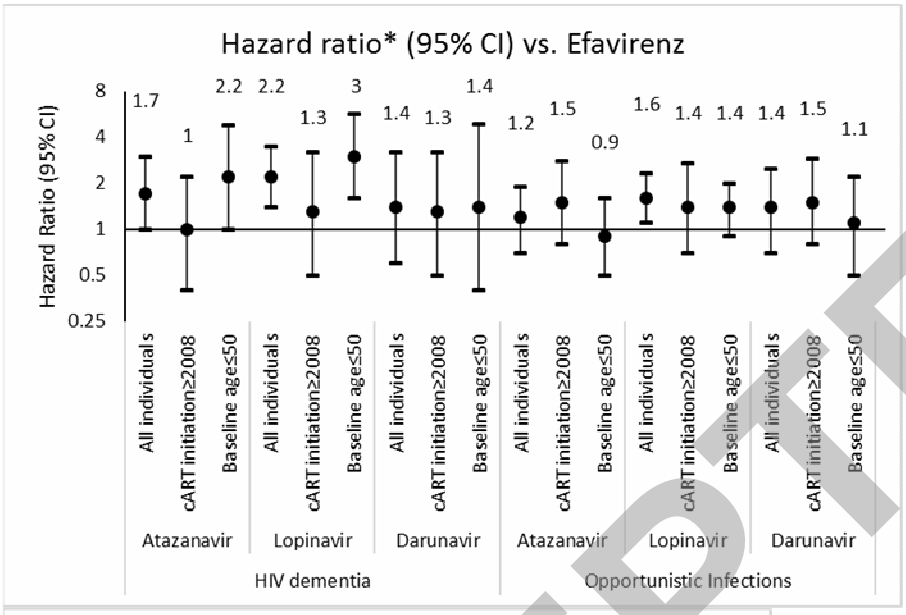
b. Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis).

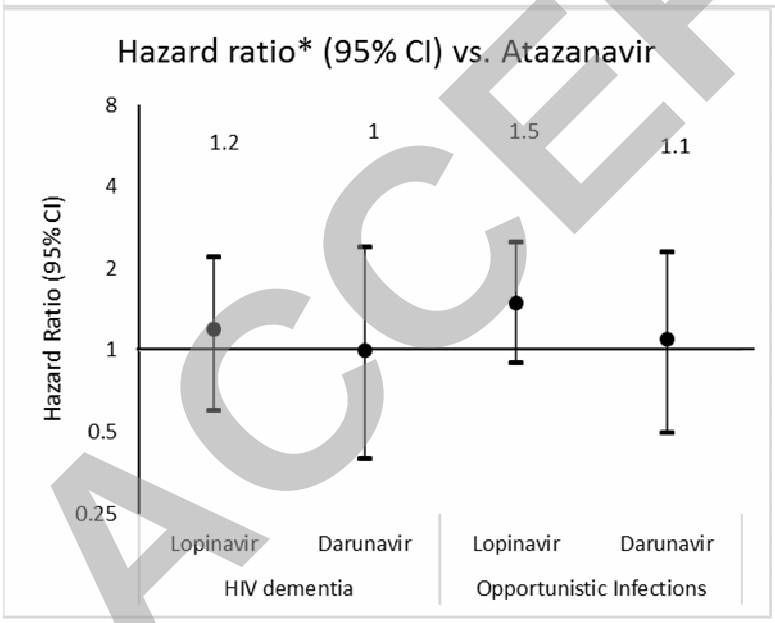
Figure 1: NeuroAIDS outcomes by recommended NRTI backbone, HIV-CAUSAL Collaboration 2004-2015.



*Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis).
TDF, tenofovir; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir. Full results in Appendix Table 1 and Appendix Figure 1.

Figure 2: NeuroAIDS outcomes by subgroup (left) and excluding efavirenz (right), HIV-CAUSAL Collaboration 2004-2015.





*Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis).
cART initiation ≥2008, analysis restricted to individuals initiating cART in 2008 or later
Baseline age≤50, analysis restricted to individuals less than 50 years at baseline
Full results in Appendix Table 2 and Appendix Table 3.